40 CFR Part 799

[OPTS-42034D; FRL-3145-6]

Ethyltoluenes, Trimethylbenzenes, and the C_9 Aromatic Hydrocarbon Fraction; Final Test Standards and Reporting Requirements

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: EPA is issuing a final test rule under section 4(a) of the Toxic Substances Control Act (TSCA) that specifies test standards and reporting requirements for testing of the C_9 aromatic hydrocarbon fraction (C_9 fraction).

DATES: In accordance with 40 CFR 23.5 (50 FR 7271; February 21, 1985), this rule shall be promulgated for purposes of judicial review at 1 p.m. eastern ("daylight" or "standard," as appropriate) time on February 6, 1987. This rule shall become effective on March 9, 1987.

FOR FURTHER INFORMATION CONTACT: Edward A. Klein, Director, TSCA Assistance Office (TS-799), Office of Toxic Substances, Rm. E-543, 401 M St., SW., Washington, DC 20460, (202) 554-1404.

SUPPLEMENTARY INFORMATION: EPA is issuing a final test rule under section 4(a) of TSCA to require specific test standards and reporting requirements be used in testing the C_9 fraction under 40 CFR 799.2175.

I. Background

This notice is part of the implementation of section 4 of TSCA (Pub. L. 94-469, 90 Stat. 2003 *et seq.*, 15 U.S.C. 2601 *et seq.*), which contains authority for EPA to require the development of data relevant to assessing the risk to health and the environment posed by exposure to particular chemical substances or mixtures.

The ITC designated ethyltoluenes (mixed isomers) and 1,2,4-trimethylbenzene for priority testing consideration in its Tenth Report, published in the **Federal Register** of May 25, 1982 (47 FR 22585), and recommended in its Eleventh Report, published in the **Federal Register** of December 3, 1982 (47 FR 54624), that the other trimethylbenzenes (1,2,3- and 1,3,5-isomers) be considered for testing. EPA responded to the ITC's designation by issuing a proposed test rule for the C_9 fraction, published in the **Federal Register** of May 23, 1983 (48 FR 23088). Subsequently, in the **Federal Register** of May 17, 1985 (50 FR 20662), EPA promulgated a final Phase I rule requiring testing of the C_9 fraction. EPA based the final testing requirements for the C_9 fraction on the authority of section 4(a)(1)(B) of TSCA. For a detailed discussion of EPA's findings and testing requirements, refer to the final Phase I rule. In accordance with the Test Rule Development and Exemption Procedures for two-phase rulemaking in 40 CFR Part 790, persons subject to this rule were required to submit letters of intent to perform the testing or exemption applications. Those submitting letters of intent were required to submit proposed study plans (including time schedules) for the testing required in the final Phase I rule.

On July 31 and August 30, 1985, U.S. manufacturers and processors of the C_9 fraction through the American Petroleum Institute (API) jointly notified EPA of their intent to sponsor the testing required in the Phase I test rule (Refs. 1 and 2). API submitted proposed study plans on September 30, 1985, and revisions to the plans on January 10, 1986. In the **Federal Register** of March 27, 1986 (51 FR 10557), EPA proposed that the study plans submitted by API, and certain additions and reporting requirements proposed by EPA, be adopted as the test standards and reporting requirements for the testing of the C_9 fraction. After review of public comments, EPA is now promulgating a final Phase II rule requiring the C_9

T-C

fraction manufacturers and processors to conduct this testing in accordance with the revised EPA-approved study plans and reporting requirements for the C_6 fraction. These study plans and reporting requirements consist of API's original study plan proposal, EPA's proposed additions and any revisions made in response to public comments. These study plans and reporting requirements are the test standards and reporting requirements for this substance.

II. Proposed Test Standards

API notified EPA by letter (Refs. 1 and 2) of its intent to conduct the testing required in the final Phase I rule for the C_6 fraction (40 CFR 799.2175) on behalf of manufacturers and processors of the C_6 fraction. API submitted proposed study plans (Refs. 3 and 4) for the required testing which, after evaluation and certain additions, EPA approved for use in testing the C_6 fraction. The study plans included the following studies: Inhalation Carcinogenesis Study in Rats and Mice, Developmental Toxicity Study in Rats and Mice, Two Generation (One Litter) Inhalation Reproduction Study in Rats, Neurotoxicity Study in Rats; the following first-tier mutagenicity studies: *In Vitro* Mammalian Cytogenetics Assay Utilizing Hamster Ovary Cells, *Salmonella typhimurium* Reverse Mutation Assay, *In Vitro* Sister Chromatid Exchange Assay Utilizing Chinese Hamster Ovary Cells, *In Vitro* Mammalian Cell Mutagenesis Assay Utilizing Chinese Hamster Ovary Cells, *In Vivo* Mammalian Bone Marrow Cytogenetics Assay in rats; the following triggered second-tier mutagenicity studies: *In Vitro* Mammalian Cell Mutagenesis Assay Utilizing Mouse Lymphoma L5178Y Cells, Sex-Linked Recessive Lethal Test in *Drosophila melanogaster*, Dominant Lethal Assay in Rats; and the following triggered end-point mutagenicity studies: Heritable Translocation Assay in Mice and Mouse Visible Specific Locus Test.

The Agency proposed these plans with the EPA-specified additions as the test standards for conducting the testing of the C_6 fraction required under 40 CFR 799.2175 in the proposed Phase II test rule for the C_6 fraction, published in the Federal Register of March 27, 1986 (51 FR 10557). The EPA-approved study plans all conformed to the appropriate TSCA Health Effects Test Guidelines (40 CFR Part 798) or contained justified deviations from the appropriate guideline. All of the testing for the C_6 fraction will be conducted in accordance with EPA's TSCA Good Laboratory Practice standards set forth in 40 CFR Part 792.

III. Proposed Reporting Requirements

Although API had proposed a schedule for testing the C_6 fraction, the Agency determined that API's schedule for some studies was inappropriate. Therefore, EPA proposed in the Phase II rule reporting requirements and a schedule for completing and submitting all final study reports for the C_6 fraction testing which differed from API's schedule.

Subsequent to the issuance of the proposed Phase II test rule for the C_6 fraction, the Agency has decided that interim reports for the testing required for substances under section 4 of TSCA be submitted at 6-month intervals, rather than at 3-month intervals, which will be sufficient to keep EPA informed of the status of required testing and of any difficulties which the testing facility may encounter during the course of testing. Accordingly, the final reporting requirements for the testing required for the C_6 fraction specify 6-month, rather than 3-month, interim testing reports.

IV. Response to Public Comments

The only comments received by the Agency in response to the proposed Phase II test rule for the C_6 fraction were from API (Ref. 5). In addition, API submitted for the Agency's consideration a developmental toxicity study conducted in Hungary on a C_6 mixture (Ref. 7). The major issues identified during the comment period are discussed below.

A. Review of Test Data

API commented that EPA should provide a public forum for review of newly generated test data before proceeding, in particular, with third-tier mutagenicity tests or with a chronic oncogenicity bioassay. API also identified several issues which it believes should be discussed in such a public review. API expressed concern that EPA's Phase II proposal for the C_6 fraction differed from aspects of the Phase I C_6 fraction final rule. The Phase I final rule indicated that after initial tier mutagenicity testing the Agency may need to assess, with public participation, the results of these studies before deciding to require higher tier testing; whereas the C_6 Phase II proposal, in API's estimation, appeared to eliminate such a step.

EPA believes this is a misunderstanding of the proposed Phase II C_6 fraction test rule. As clearly stated in the final Phase I rule regarding triggering the end-point mutagenicity testing and oncogenicity testing (50 FR 20669 and 20672, respectively), EPA will provide for public participation in certain circumstances.

Before the last tier mutagenicity testing is to begin, EPA will hold a public review if the results of the previous tier tests are positive. If, after review of public comment, no change in the test sequence is deemed necessary, EPA will provide formal notification to the test sponsor that the final tier tests should be conducted. If, however, EPA believes additional testing is no longer warranted as a result of the earlier test results, public comment, scientific judgment, and other appropriate factors, EPA will issue a proposed amendment to rescind these requirements.

Regarding triggered oncogenicity testing, EPA promulgated the rule with the triggered chronic bioassay if any of the specified short-term tests fails to produce a negative result. If results of one or more tests are clearly positive, EPA will notify the test sponsors to initiate the chronic study. However, if mixed negative and equivocal results (i.e., non-negative response) are obtained, the Agency will review the overall weight of scientific evidence provided by all of the tests. If, in EPA's judgment, that evidence indicates that oncogenicity of the C_6 fraction is quite unlikely, the Agency will solicit public comment on whether it should rescind the requirement for the chronic test.

B. Mouse Specific Locus Assay

API commented that the lack of available laboratories for conducting the mouse specific locus assay complicates API's ability to produce these test data. API requested that the availability of qualified testing facilities be reexamined during the public program review of the mutagenicity data.

Currently, Oak Ridge National Laboratory is available for direct contracting of this testing. The testing can be performed according to EPA's Good Laboratory Practice Standards with personnel and funds provided by the test sponsor. Other laboratories may be available at the time this testing becomes necessary. In any case, the issue raised by API will be considered by the Agency in the public program review of the mutagenicity data for the C_6 fraction which, as described in the final Phase I test rule for the C_6 fraction, will precede the initiation of the testing of the C_6 fraction in the mouse specific locus test. If EPA believes the testing is no longer warranted as a result of the earlier test results, public comment, scientific judgment, and other appropriate factors, EPA will issue a

T-9

proposed amendment to rescind the requirement.

C. Repeating Mutagenicity Assays

API commented that it is inappropriate to include a generic requirement to repeat all mutagenicity assays, particularly *in vivo* assays, in which a single, statistically significant elevated response is detected without a dose response. API believes that an unusually elevated response in an *in vitro* assay at a single data point, in the absence of a dose response, warrants a repeat assay over a dose range designed to bracket the dose of interest and generate a dose-response curve. API believes a weight-of-evidence approach should be applied prior to initiation of repeat studies for *in vivo* studies.

The Agency has reconsidered the need to require repeats of mutagenicity assays and agrees that a generic requirement to repeat the *in vivo* assays is not routinely necessary. The Agency will, however, interpret any single positive finding as a positive mutagenic response in the absence of a repeat assay. The Agency is therefore not including a requirement for repeats of the following assays: *in vivo* mammalian cytogenetics, Drosophila sex-linked recessive lethal, rodent dominant lethal, rodent heritable translocation, and mouse visible specific locus. Because of the nature of *in vitro* tests in comparison to *in vivo* systems, the Agency believes that repeats are appropriate and necessary for the evaluation of the *Salmonella typhimurium* reverse mutation, *in vitro* sister chromatid exchange, *in vitro* mammalian cell mutagenesis, and *in vitro* mammalian cytogenetics assays. The Agency is thus requiring repeats of these assays over a narrow range of concentrations in the event a single, statistically significant positive effect is produced at one dose point without a dose response.

D. Non-Negative Results Triggering Oncogenicity Testing

API does not believe that an oncogenicity bioassay should be considered based on anything less than a fully positive response in the mutagenicity assays.

The final Phase I rule for the C_o fraction requires that an oncogenicity study be performed with the C_o fraction if any of the specified short-term tests fails to produce a negative result. API's comments did not alter EPA's belief that only clearly negative responses in all of several short-term genotoxicity tests provide sufficient basis to rule out the need for a lifetime bioassay to determine the potential for oncogenicity of a large-exposure chemical such as the C_o fraction. As stated in the Final Phase I rule for the C_o fraction, in the event mixed negative and equivocal results are obtained, the Agency will review the overall weight of evidence provided by all the tests and, if testing no longer appears warranted, will solicit public comment on whether to rescind the requirement for the bioassay.

E. Timing for Studies

API commented that the reporting and study timing requirements proposed by EPA were, for the most part, acceptable. API noted a few exceptions, however, and suggested that: (1) reporting requirements for the second and third tier mutation studies be measured from the submission of results of previous mutagenicity testing, rather than from the effective date of the rule; (2) the mouse specific locus assay be completed in 48 months, rather than 24 months; (3) the inhalation developmental toxicity study be completed and a final report submitted to EPA within 18 months, rather than 12 months, from the effective date of the rule; and (4) the neuropathology testing be completed and the study results submitted to EPA within 25 months, instead of 15 months, from the effective date of the rule.

EPA does not agree with API's comment that the reporting requirements for the second-tier mutagenicity assays should be measured from the submission of results of the first-tier assays. EPA believes these second-tier studies, i.e., *in vitro* mammalian cell mutagenesis assay, sex-linked recessive lethal assay, and dominant lethal assay, have relatively short performance times that can be accommodated in the 24-month period from the effective date of the rule. In establishing the time period, EPA also included the possibility of repeating assays. Because EPA has established a clear definition for positive and negative results in these tests, there should be no reason for delays in their progress. If necessary, API may request modification to any test standard or schedule during the conduct of testing through the procedures described in 40 CFR 790.55 in the event of unforeseen problems that might justify an extension.

Regarding the reporting requirements for the third-tier mutagenicity studies, the Agency does agree that the time period allowed for testing may be significantly shortened under the proposed reporting requirement for these assays should some unforeseen circumstances lengthen the period required for EPA's public program review. In view of this possibility, the EPA is specifying in the final Phase II test rule that the time period for submission of the final report resulting from the testing of this substance in the heritable translocation assay and the mouse specific locus assay will be measured from the date of EPA's notification of the test sponsor by certified letter or Federal Register notice of the Agency's decision that testing should be initiated. Such notification will follow a public program review of the then available data for the C_o fraction resulting from a positive test result for this substance in the second-tier studies and a decision that the required testing must be initiated.

Regarding the time period for conduct of the mouse specific locus assay, EPA agrees that a 48-month period is appropriate for this testing and submission of the final report. The Agency acknowledges that the 24-month time period proposed underestimated the amount of time necessary to conduct this assay.

Regarding the reporting requirement for the inhalation developmental toxicity testing, EPA agrees that an 18-month period is appropriate for this testing. The Agency recognizes that development of a method of producing a stable target vapor concentration for the C_o fraction and of a sampling and analysis method will extend the time for testing.

Lastly, EPA agrees with API to extend the study period and reporting time for the neuropathology testing. EPA believes that 15 months, as proposed, should be sufficient for conducting and reporting on the motor activity test and the functional observation studies. However, recognizing the effort necessary to complete neuropathology examinations, according to the study plans proposed for the testing of the C_o fraction, EPA accepts API's arguments to extend the reporting period for the neuropathology examinations. Therefore, considering a 4- to 6-month chamber validation and dose level finding study, a 4-month in-life study phase (90 days plus 30 days post-exposure observation period), and 12 months for neuropathological examinations, EPA agrees that final study results will be reported within 25 months from the effective date of this rule.

F. Oncogenicity Study

API requested that EPA clarify the time period specified for the duration of the in-life portion of the study. EPA has modified the language to specify a time period of not less than 24 months for rats and 18 months for mice. This

T-7

T-10

conforms with the TSCA Test Guidelines for Oncogenicity.

API also commented that EPA's proposal that food and water consumption data be reported does not apply for an inhalation study. EPA has modified the requirement to specify that food and water consumption data shall be reported if measured. This conforms with the TSCA Test Guidelines for Oncogenicity.

G. Revised Neurotoxicity Battery

Since submitting its proposed study plan, API has identified in its comments (Ref. 5) to the proposed Phase II rule for the C_9 fraction (revised in a subsequent submission (Ref. 6)) a battery of observational tests that API believes more quantitatively measures functional impairment than those it had originally proposed for study. API believes these studies (Ref. 6) should be used in lieu of the functional observation battery previously submitted (Ref. 3). Aside from the motor activity test, API proposed to replace the functional observation studies outlined in its Proposed Study Plan. A brief description of each of the studies proposed by API to replace the originals is provided below:

1. *Righting reflex and visual placing.* In lieu of the righting reflex and visual placing assays, API proposed to use a measurement of foot splay. In this measurement, the animal's hind feet are marked in India ink and the animal is dropped 32 centimeters (cm) onto a blotter. Subsequently, the distance between the digits is measured and provides a quantitative assessment of motor coordination. Visual placing is also required for the animal to land properly.

2. *Tail pinch.* Rather than the tail pinch study, API proposed to measure thermal response time. In this assay, an animal is placed on a warm surface. The time from being placed on the plate to when the animal begins to lick his feet is recorded and provides a quantitative measure of the animal's response to an external stimulus.

3. *Startle response.* API proposed to measure the startle response quantitatively by measuring the time from the initiation of a noise to animal response and the intensity of response, using a device specifically designed to perform these measurements.

4. *Grip strength.* API proposed to quantitatively measure both fore and hind limb grip strength using strain gauges.

EPA believes these methods are reasonable for measuring motor activity in functional observation studies and is adopting them in this final Phase II test rule as the test standards for the functional observation testing of the C_9 fraction. EPA believes that the foot splay measurement is a more easily quantified study than the righting reflex originally proposed by API. While the extent to which the same functions are tapped by these different tests is not clear, it is difficult to imagine a situation in which the original tests would produce findings which would not be accompanied by similar findings on the foot splay test. EPA also believes that replacing the tail pinch test with a thermal response test is a good substitution for two reasons. First, it is more quantitative than the tail pinch test. Second, since it probably involves supraspinal mechanisms in addition to spinal mechanisms, it may detect more types of dysfunction than the tail pinch. Finally, EPA believes the use of devices designed to measure the elapsed time and intensity of response from noise initiation to animal response for the startle response test, and strain for the grip strength test should increase the quantitative aspects of these studies as well.

H. Test Sample

API, in responding to proposed Agency requirements for test substance identity, source, and stability, plans to characterize the components of the test material as well as the atmosphere that is inhaled by the test animals. Vapor phase concentrations will be routinely monitored as described in API's study plan to determine total hydrocarbon content. In addition, analytical methods will be developed by API to identify and quantify all of the test material components that are greater than 5 percent by weight of the total mixture. API plans to conduct the identification and quantification analyses once each week for the first month for all inhalation studies and then once monthly for the remainder of the studies.

EPA agrees that verifiable quantitative analytical procedures, in combination with the measurements described in the API study plan revisions (Ref. 5) under physical measurements, should provide sufficient confirmation and identification of the test atmosphere in both the inhalation developmental toxicity and oncogenicity studies.

I. Developmental Toxicity

In addition its public comments on the C_9 fraction proposed Phase II test rule, API submitted a rat inhalation developmental toxicity study on a C_9 mixture called Aromatol (Ref. 7). The C_9 test material, containing 38 percent ortho-, meta-, and para-ethyltoluene and 48 percent 1,2,4-, 1,2,3-, and 1,3,5-trimethylbenzene and intended for use as a solvent, appears to meet the definition of the test substance specified in the final Phase I test rule for the C_9 fraction. In the study, pregnant CFY rats were administered the C_9 mixture at 0, 600, 1,000, and 2,000 mg/m^3 for 24 hours per day on gestation days 7 to 15. Maternal toxicity was observed at 2,000 mg/m^3. Decreased male body weight and decreased skeletal and soft tissue development were observed in offspring (day 21) in the absence of maternal toxicity. The no observed effect level (NOEL) was 600 mg/m^3. In offspring necropsied on postnatal day 90, no postnatal functional defects were observed.

The study plan submitted by API and the proposed Phase II rule called for developmental toxicity testing of the C_9 fraction in two animal species. However, EPA has reviewed the study discussed above (Ref. 7) and finds it adequate to characterize the developmental toxicity of the C_9 fraction in one species. Thus, EPA believes there is no need to develop additional data for the rat. However, to fully characterize the developmental toxicity of the C_9 fraction, additional data in a second species are still needed. Therefore, EPA is adopting in this final rule the proposed study plan submitted by API for developmental toxicity in mice, but is not requiring the proposed developmental toxicity study in rats.

V. Final Phase II Test Rule

A. Test Standards

The test protocols contained in the approved study plans for the C_9 fraction for mutagenicity, oncogenicity, developmental toxicity in mice, and reproductive effects testing (Refs. 3 and 4) and for neurotoxicity testing (Ref. 6) and the additional requirements specified in 40 CFR 799.2175 are the test standards for the testing of the C_9 fraction required under 40 CFR 799.2175. The Agency believes that the conduct of the required tests in accordance with the approved study plans will ensure that the resulting data are reliable and adequate. The testing must be conducted in accordance with the EPA's TSCA Good Laboratory Practice Standards (40 CFR Part 792).

B. Reporting Requirements

The Agency is requiring that all data developed under this rule be reported in accordance with the TSCA Good Laboratory Practice Standards (40 CFR Part 792).

T-10

T-11

The Agency is required by TSCA section 4(b)(1)(C) to specify the time periods during which persons subject to a test rule must submit test data. On the basis of the Agency's regulatory experience for the tests required for the C_9 fraction, as well as in response to certain public comments, EPA is adopting the reporting requirements for these tests as presented below.

REPORTING REQUIREMENTS FOR THE C_9 FRACTION

Test	Reporting deadline for final report [1]	Number of interim (6-mo.) reports required
Salmonella reverse mutation assay	12	1
In vitro sister chromatid exchange assay	12	1
Gene mutation cells in culture assay	12	1
Second gene mutation in mammalian cells in culture assay	24	3
Sex-linked recessive lethal test in *Drosophila*	24	3
Mouse specific locus assay	[2] 48	7
In vitro cytogenetics test	12	1
In vivo cytogenetics test	12	1
Dominant lethal test	24	3
Heritable translocation assay	[2] 24	3
Oncogenicity (inhalation)	[2] 53	8
Inhalation developmental toxicity	18	2
Reproductive effects	28	4
Neurotoxicity battery for functional observation and motor activity	15	2
Neuropathology	25	3

[1] Months after the effective date of final phase II rule, except as indicated.
[2] Figure indicates the reporting deadline, in months, calculated from the date of notification of the test sponsor by certified letter or Federal Register notice that, following public program review of all of the then existing data for the C_9 fraction, the Agency has determined that the required testing must be performed.
[3] Figure indicates the reporting deadline, in months, calculated from the date of notification of the test sponsor by certified letter or Federal Register notice that, following submission of nonnegative mutagenicity test results, the Agency has determined that the required testing must be performed.

As required by TSCA section 4(d), the Agency will publish in the Federal Register a notice of the receipt of any test data submitted under this test rule within 15 days after receipt of the data. Except as otherwise provided in TSCA section 14, such data will be made available for examination by any person.

C. Conditional Exemptions Granted

The final rule for test rule development and exemption procedures (40 CFR 790.87) indicates that, when certain conditions are met, exemption applicants will be notified by certified mail or in the final Phase II test rule for a given substance that they have received conditional exemptions from test rule requirements. The exemptions granted are conditional because they will be given based on the assumption that the test sponsors will complete the required testing according to the test standards and reporting requirements established in the final Phase II test rule for the given substance. TSCA section 4(c)(4)(B) provides that if an exemption is granted prospectively (that is, on the basis that one or more persons are developing test data, rather than on the basis of prior test data submissions), the Agency must terminate the exemption if any test sponsor has not complied with the test rule.

Since sponsors have indicated to EPA by letters of intent (Refs. 1 and 2) their agreement to sponsor all of the tests required for the C_9 fraction in the final Phase I test rule for this substance (50 FR 20662; May 17, 1985) and EPA had adopted test standards and reporting requirements in this final Phase II test rule for the C_9 fraction, the Agency is hereby granting conditional exemptions to all exemption applicants for all of the testing required for the C_9 fraction in 40 CFR 799.2175.

D. Judicial Review

The promulgation date for the final Phase I test rule for the C_9 fraction was established as 1 p.m. eastern daylight time on June 3, 1985 (50 FR 20662; May 17, 1985). To EPA's knowledge, no petitions for judicial review of that Phase I final rule were filed. Any petition for judicial review of this final Phase II test rule for the C_9 fraction will be limited to a review of the test standards and reporting requirements for this substance which are established in this final rule.

E. Other Provisions

TSCA section 4 findings, required testing, test substance specifications, persons required to test, enforcement provisions, and the economic analysis are all presented in the final Phase I test rule for the C_9 fraction (50 FR 20662; May 17, 1985).

VI. Public Record

A. Supporting Documentation

EPA has established a record for this rulemaking [docket number OPTS-42034D]. This record includes the basic information considered by the Agency in developing this rule and appropriate Federal Register notices.

B. References

(1) American Petroleum Institute. Letter from William F. O'Keefe to TSCA Public Information Office, USEPA. July 31, 1985.
(2) American Petroleum Institute. Letter from William F. O'Keefe to TSCA Public Information Office. USEPA. August 30, 1985.
(3) American Petroleum Institute. Proposed Study Plan for Toxicity Testing of Ethyltoluenes, Trimethylbenzenes and the C_9 Aromatic Hydrocarbon Fraction. September 30, 1985.
(4) American Petroleum Institute. Letter from William F. O'Keefe to TSCA Public Information Office, USEPA. January 10, 1986.
(5) American Petroleum Institute. Letter with attachments from William F. O'Keefe to Gary Timm, Test Rules Development Branch, USEPA. May 15, 1986.
(6) American Petroleum Institute. Letter from Steven M. Swanson to Nancy Merrifield, USEPA. November 4, 1986.
(7) Ungvary, G., Tatrai, E., Lorinez, M., Fittler, Z., Barcza, G. "Investigation of the Embriotoxic Effects of Aromatol, a New C_9 Aromatic Mixture" (translation from Hungarian). *Health Science* 27:138–148. (1983).

The record is available for inspection from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays, in Rm. G-004, NE Mall, 401 M St., SW., Washington, DC 20460.

VII. Other Regulatory Requirements

A. Executive Order 12291

Under Executive Order 12291, EPA must judge whether a regulation is "major" and, therefore, subject to the requirements of a Regulatory Impact Analysis. This test rule is not major because it does not meet any of the criteria set forth in section 1(b) of the Order. The economic analysis of the testing required for the C_9 fraction is discussed in the Phase I test rule (50 FR 20662; May 17, 1985).

11-7

T-12

This final Phase II test rule was submitted to the Office of Management and Budget (OMB) for review as required by Executive Order 12291. Any written comments received from OMB, together with any EPA response to these comments, are included in the public record for this rulemaking.

B. Regulatory Flexibility Act

Under the Regulatory Flexibility Act (15 U.S.C. 601 *et seq.*, Pub. L. 96-354, September 19, 1980), EPA is certifying that this test rule, if promulgated, will not have a significant impact on a substantial number of small businesses for the following reasons:

1. There is not a substantial number of small businesses manufacturing the C_9 fraction.

2. Small manufacturers of the C_9 fraction are not expected to perform testing themselves.

3. Small manufacturers of the C_9 fraction will experience only small reimbursement costs.

4. Small processors of the C_9 fraction are not expected to perform testing themselves or to participate in the organization of the testing efforts.

5. Small processors are unlikely to be affected by reimbursement requirements.

C. Paperwork Reduction Act

OMB has approved the information collection requirements contained in this rule under the provisions of the Paperwork Reduction Act of 1980, 44 U.S.C. 3501 *et seq.*, and has assigned the OMB control number 2070-0033. No public comments on the requirements contained in the proposed Phase II rule for the C_9 fraction (51 FR 10557; March 27, 1986) were submitted to the Office of Information and Regulatory Affairs of OMB.

List of Subjects in 40 CFR Part 799

Testing, Environmental protection, Hazardous substances, Chemicals, Recordkeeping and reporting requirements.

Dated: January 13, 1987.

John A. Moore,

Assistant Administrator for Pesticides and Toxic Substances.

PART 799—[AMENDED]

Therefore, Chapter I of 40 CFR Part 799 is amended as follows:

1. The authority citation for Part 799 continues to read as follows:

Authority: 15 U.S.C. 2603, 2611, 2625.

2. In § 799.2175 by revising paragraphs (d)(1)(ii), (2)(ii), (3)(ii), (4)(ii), (5)(ii), and (6)(ii), and adding paragraphs (e) and (f), to read as follows:

§ 799.2175 C_9 aromatic hydrocarbon fraction.

* * * * *

(d) * * *

(1) * * *

(ii) *Reporting requirements.* (A) The mutagenic effects testing for chromosomal aberrations as contained in the first tier of testing, which consists of an *in vitro* cytogenetics test and an *in vivo* cytogenetics test shall be completed and the final results submitted to the Agency within 12 months of the effective date of the final Phase II rule.

(B) The mutagenic effects testing for chromosomal aberrations as contained in the second tier of testing, which consists of a dominant lethal assay, shall be completed and the final results submitted to the Agency within 24 months of the effective date of the final Phase II rule.

(C) The mutagenic effects testing for chromosomal aberrations as contained in the third tier of testing, which consists of a heritable translocation assay, shall be completed and the final results submitted to the Agency within 24 months of the date of EPA's notification of the test sponsor by certified letter or Federal Register notice that testing should be initiated.

(D) Progress reports shall be submitted to the Agency for the *in vitro* and *in vivo* cytogenetics assays and the dominant lethal assay at 6-month intervals, the first of which is due within 6 months of the effective date of the final Phase II rule.

(E) Progress reports shall be submitted to the Agency for the heritable translocation assay at 6-month intervals, the first of which is due within 6 months of the date of EPA's notification of the test sponsor that testing should be initiated.

(2) * * *

(ii) *Reporting requirements.* (A) The mutagenic effects testing for gene mutations as contained in the first tier of testing, which consists of a *Salmonella typhimurium* mammalian reverse mutation microsomal assay, a sister chromatid exchange (SCE) assay, and a gene mutation in mammalian cells in culture assay, shall be completed and the final results submitted to the Agency within 12 months of the effective date of the final Phase II rule.

(B) The mutagenic effects testing for gene mutations as contained in the second tier of testing, which consists of a second gene mutation in mammalian cells in culture assay and a *Drosophila* sex-linked recessive lethal test, shall be completed and the final results submitted to the Agency within 24 months of the effective date of the final Phase II rule.

(C) The mutagenic effects testing for gene mutations as contained in the third tier of testing, consisting of a mouse specific locus assay, shall be completed and the final results submitted to the Agency within 48 months of the date of EPA's notification of the test sponsor by certified letter or Federal Register notice that testing should be initiated.

(D) Progress reports shall be submitted to the Agency for the *Salmonella typhimurium* mammalian reverse mutation microsomal assay, SCE assay, gene mutation in mammalian cells in culture assays, and *Drosophila* sex-linked recessive lethal test at 6-month intervals, the first of which is due within 6 months of the effective date of the final Phase II rule.

(E) Progress reports shall be submitted to the Agency for the mouse specific locus assay at 6-month intervals, the first of which is due within 6 months of the date of EPA's notification of the test sponsor that testing should be initiated.

(3) * * *

(ii) *Reporting requirements.* (A) The oncogenicity testing shall be completed and the final results submitted to the Agency within 53 months after the date of EPA's notification of the test sponsor by certified letter or Federal Register notice that testing should be initiated.

(B) Progress reports shall be submitted to the Agency at 6-month intervals, the first of which is due within 6 months after the date of EPA's notification of the test sponsor that testing should be initiated.

(4) * * *

(ii) *Reporting requirements.* (A) The developmental toxicity testing shall be completed and the final results submitted to the Agency within 18 months of the effective date of the final Phase II rule.

(B) Progress reports shall be submitted to the Agency at 6-month intervals, the first of which is due within 6 months from the effective date of the final Phase II rule.

(5) * * *

(ii) *Reporting requirements.* (A) The reproductive effects testing shall be completed and the final results submitted to the Agency within 29 months of the effective date of the final Phase II rule.

(B) Progress reports shall be submitted to the Agency at 6-month intervals, the first of which is due within 6 months from the effective date of the final Phase II rule.

(6) * * *

(ii) *Reporting requirements.* (A) The neurotoxicity test battery consisting of a

T-13

motor activity test and functional observational battery shall be completed and the final results submitted to the Agency within 15 months from the effective date of the final Phase II rule.

(B) The neuropathology test shall be completed and the final results submitted to the Agency within 25 months from the effective date of the final Phase II rule.

(C) Progress reports shall be submitted to the Agency at 6-month intervals, the first of which shall be due within 6 months from the effective date of the final Phase II rule.

(e) *Test standards*—(1) *General.* (i) The required testing specified in paragraphs (d) (1), (2), (3), (4), and (5) of this section shall be conducted in accordance with the study plans for testing the C_9 fraction developed by the American Petroleum Institute (API), and submitted to the Agency on September 30, 1985, and modified in a submission dated January 10, 1986, and the additional requirements specified in this paragraph.

(ii) The required testing specified in paragraph (d)(6) of this section shall be conducted in accordance with the study plan for testing the C_9 fraction developed by API, and submitted to the Agency on November 4, 1986.

(iii) Copies of the API study plans are located in the public record for this rule (Docket No. OPTS-42034) and are available for inspection in EPA's OPTS Reading Rm., NE-G004, 401 M St., SW., Washington, DC 20460, from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays.

(2) *Mutagenic effects.* (i) For each study specified in paragraphs (d) (1)(i)(A) and (2)(i) (A), (B), (C), and (D) of this section, the study shall be repeated over a narrow range of concentrations if a single, statistically significant positive effect for at least one of the test points is produced where no statistically significant dose-related increase in the number of mutagenic events was found.

(ii) For each study specified in paragraph (d) of this section, in addition to the criteria for determining a positive result given in the study plans specified in paragraph (e)(1) of this section, the detection of a reproducible and statistically significant response for at least one of the test substance concentrations shall be interpreted as a positive result. In the absence of a repeat assay, a statistically significant response for at least one of the test substance concentrations shall be interpreted as a positive response.

(iii) For the mouse heritable translocation assay specified in paragraph (d)(1)(i)(D) of this section, the following are required.

(A) If the laboratory's historical control data base is inadequate, concurrent positive and negative controls shall be conducted which conform to the requirements specified in § 798.5200(d)(4)(i) of this chapter.

(B) Control data shall be presented, whether they are historical or concurrent, in the final report of the study and shall be identified as either the one or the other.

(3) *Oncogenicity*—(i) *Dose levels and dose selection.* The lowest dose shall not be lower than 10 percent of the high dose.

(ii) *Duration.* Each study shall last the majority of the normal lifespan of the strain of animals to be used. This time period shall not be less than 24 months for rats and 18 months for mice, and ordinarily not longer than 30 months for rats and 24 months for mice.

(iii) *Histopathology.* Target organs (including but not limited to lungs and respiratory tract) in all animals shall be subject to a histopathological examination.

(iv) *Individual animal data.* (A) Food and water consumption data shall be reported, when measured.

(B) Ophthalmological data shall be recorded when the examination is performed.

(4) *Developmental toxicity.* (i) Testing in one mammalian species other than the rat is required.

(ii) Dams shall be killed before parturition.

(5) *Test substance*—(i) *Identity and source.* The remaining components, which may be as high as 25 percent of the test mixture, shall be characterized.

(ii) *Stability under test and storage conditions.* The atmosphere being inhaled by the animals shall be characterized with regard to concentration and identification of the components inhaled.

(f) *Effective date.* The effective date of the final Phase II rule for the C_9 aromatic hydrocarbon fraction is March 9, 1987.

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T-14